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(54) Sustained release composition

(57) The composition comprises an active agent in admixture with (a) microcrystalline cellulose and (b) hydroxypropyl methylcellulose wherein the weight ratio of (a) to (b) is at least 1 to 1. Aspirin is the preferred active agent.

SPECIFICATION

Sustained release pharmaceutical compositions

This invention relates to sustained release pharmaceutical compositions.

We have surprisingly found that a solid oral sustained release formulation may be produced from the readily available and widely approved excipients microcrystalline cellulose and hydroxypropyl methylcellulose.

The invention accordingly provides in one aspect a sustained release pharmaceutical composition comprising a pharmacologically active agent in admixture with a) microcrystalline cellulose and b) hydroxypropyl methylcellulose wherein the weight ratio of a) to b) is at least 1 to 1. With the proviso that when the active agent is other than acetylsalicylic acid in free form or salt form the active agent is also in admixture with pregelatinized starch.

In another aspect the invention provides a process for the production of a sustained release pharmaceutical composition which comprises mixing a pharmacologically actige agent and a) microcrystalline cellulose and b) hydroxypropyl methylcellulose wherein the weight ratio of a) to b) is at least 1 to 1. With the proviso that when the active agent is other than acetylsalicylic acid in free form or salt form the active agent is also in admixture with pregelatinized starch.

A wide variety of pharmacologically active agents (hereinafter "agents") may be used. These may include water-soluble or water-insoluble compounds. The agents may be moisture sensitive or not. The dosage of agent may vary between wide limits.

Representative active agents include analgesics, anti-pyretics, anti-inflammatories, anti-histamines, anti-hypertensives, vasodilators, tranquillizers, anti-depressants, neuroleptics, vasoconstrictors, anti-convulsants, anti-asthmatics; etc.

The invention is exemplified hereinafter by reference to acetylsalicylic acid (hereinafter ASA) but it is to be understood that it is applicable to any active agent.

The ASA is preferably in the form of the free acid. Alternatively it may be in the form of a salt, e.g. a sodium or calcium salt. The ASA is preferably in the form of fine crystals e.g. of particle size under 40 mesh, e.g. 5 to 40 mesh.

Preferably the mean polymerisation number of the microcrystalline cellulose is from about 200 to 2000, preferably 200 to 300. Preferred mean molecular weights are from about 20,000 to about 100,000 e.g. 30,000 to 50,000. Preferably the mean particle size is from about 5 to about 140 microns. Preferably the particle size-form 20 to 100 microns, e.g. to 80 microns. Conveniently the specific gravity is about 1.40 to 1.60. Conveniently the microcrystalline cellulose is obtained by mechanical treatment of glucose-based polysaccharides, e.g. native cellulose, optionally with acidic treatment.

Preferred forms are the AVICEL brand (Registered Trade Mark of FMC Corporation).

Conveniently the methoxy content of the hydroxypropyl methylcellulose is from about 15 to about 34 per cent by weight, preferably from about 19 to 30, especially 19 to 24, per cent by weight. Preferably the hydroxypropyl content is from about 4 to about 32 per cent by weight, preferably from 4 to 12 per cent by weight.

The viscosity of the hydroxyproyl methylcellulose is conveniently from about 15 to about 50,000 cps (based on a 2 per cent by weight aqueous solution at 20 degrees centigrade) e.g. 4000 to 50,000 cps.

Conveniently the mean molecular weight is from about 20,000 to 200,000, e.g. 90,000 to 130,000.

Preferred forms of hydroxypropyl methylcellulose are those available under the brand names of Methocel A, K and E from the Dow Chemical Company Michigan.

Preferably the weight ratio of microcrystalline cellulose to hydroxypropyl methylcellulose is from about 10:1 to 1:1, e.g. 3:1 to 1:1, e.g. 3:1 to 2:1.

Preferably the weight ratio of microcrystalline cellulose to agent is from 1:5 to 1:10, e.g. 1:6 to 1:7.5, especially 1:6.5 to 1:7. Conveniently pregelatinized starch is present. Conveniently the starch is soluble to an extent of about 5 to 25, e.g. 10 to 20, per cent by weight in cold water. Suitably the pregelatinized starch is made by reacting starch, preferably corn starch (based on 80 per cent amylopectin moieties and 20 per cent amylose moieties) so as to break down hydrogen bonding between the amylose and amylopectin moieties therein. Conv niently the product contains from 60 to 85 per cent by weight of corn starch, th remainder being free amylose and amylopectin.

Preferably the weight ratio of pregelatinized starch to hydroxypropyl methylcellulose is from about 1:1 to about 1:5, e.g. to about 1:2.

Naturally other excipients may be present. These excipients may be those conv ntionally used in pharmaceutical formulations, such as anti-frictional agents, e.g. lubricants such as stearic acid or magnesium stearate, and glidants such as silicon dioxide, anti-adherents, soluble fillers such as lactose, flavouring agents and colourants.

Conveniently the weight ratio of agent to all other excipients present is from about 0.2:1 to

about 0.4:1, e.g. from about 2:1 to 4:1. Conveniently the hydroxypropyl methylcellulose content is from about 5 to 10 per cent of the total weight, e.g. 6 to 9 per cent, especially 6.5 or 8.5 per cent.

The pharmaceutical composition is preferably in solid form. Preferably it is in a unit dose form. Conveniently it is in the form of a tablet.

Conveniently the amount of ASA per unit dose is from 300 to 400 mg or 600 to 700 mg. Such pharmaceutical compositions may be produced by techniques well known in the art.

Tablets are preferably compressed to a hardness of from about 8 to 12 kiloponds (based on the Heberlein method).

The bioavailability of the compositions of the invention may be determined in conventional manner.

In a typical trial ASA pharmaceutical compositions of the invention are administered at 7 am, 3 pm, 11 pm or 7 am and 7 pm. Immediate release ASA compositions are administered at 7 am, 11 am, 3 pm, 7 pm and 11 pm, as reference formulations.

Free and total salicylic acid (SA) may be measured in conventional manner by HPLC (essentially that of Hamson et al, J.Pharm.Sci. (1980) *69* 1268).

Free SA detection method

Heparinized blood samples are collected. Plasma is separated within 15 minutes of drawing blood, divided into 2 portions and placed in polypropylene tubes sealed with colour-coded polypropylene plugs.

0.5 ml Samples are acidified with 1 drop of concentrated phosphoric acid for a few minutes, and extracted with toluene/ethyl acetate (50:50). The extracts are analysed using reverse phase HPLC with UV detection at 305 mm using 3,4-dimethoxy-benzoic acid as internal standard. The method gives a minimum quantifiable level of 0.1 microgram per millilitre of free SA.

Total SA detection method

Total SA is determined from urine as salicylic acid. Each 1 ml urine sample was mixed with 1 ml of concentrated hydrochloric acid, sealed and heated for 16 hours at 98°C. The sample is allowed to cool. 1 ml acetonitrile is added containing the internal standard. The samples are subjected to HPLC analysis and the SA detected by ultra-violet spectroscopy at 313 mm.

The bioavailability trials are preferably continued for at least eight days. Further details are apparent from the trials described hereinafter. The measured mean salicylate concentrations show an unexpectedly high availability of free salicylate in the blood from the pharmaceutical compositions of the invention, especially at anti-inflammatory therapeutic levels.

The trials as described hereinafter show the non-linearity of ASA kinetics since the 0–8 hour AUC for free salicylate for a dose of 3.9 gram ASA (1300 mg ASA given 3 times a day in Trial A) at a dose of 3.9 g ASA is disproportionately higher than that for 2.6 gram ASA (1300 mg given twice a day in Trial B). The urine excretion data show that for doses of 2.6 g ASA and 3.9 g ASA the cumulation excretion of total SA is similar and indepedent of dose.

These results suggest that at high doses of ASA at which an anti-inflammatory effect occurs there is a constant saturation of metabolic pathways (as indicated by the dose-independent cumulative urinary excretion values). We have found that the plasma concentration of free SA increases disproportionately to the dose at high doses of ASA. We believe that this may be due to a combination of the effect of clearance of the unbound ASA and the ratio of protein-bound SA to unbound SA in plasma. When metabolism is saturable clearance should decrease but when protein binding is saturated clearance increases. Therefore the steady state concentration of free SA may depend on the magnitude of each of these two effects.

The pharmaceutical compositions of the invention have a longer elimination half life (e.g. greater than 9 hours) than that of immediate release ASA pharmaceutical compositions. In the case of immediate release ASA compositions large peak-to-trough ratios of free SA may occur which may provide periods of increased metabolism of SA resulting in lower steady state levels. The pharmaceutical compositions of the invention on the other hand provide therapeutic concentrations of SA at lower daily doses than immediate release ASA pharmaceutical compositions, and have less GI-irritating potential.

The pharmaceutical compositions of the invention may be administered for all indications that ASA is indicated for, in particular pains of rheumatism, arthritis, lumbago, neuralgia, neuritis, sciatica and bursitis (anti-inflammatory indications), fever and cerebral ischemic attacks.

For anti-inflammatory indications a dose of about 600 to 1300, e.g. 650 to 1300 mg, ASA every 8 to 12 hours is satisfactory. Daily doses contemplated are from about 2.6 to about 3.9 g. Analgesic and anti-pyretic indicated doses are from about 300 to about 700 mg, e.g. 325 to 650 mg. For rheumatic fever daily doses of 100 mg ASA/kg body weight may be given in divided doses every 8 to 12 hours to counteract pain, swelling and fever. For cerebral ischemic attacks an indicated dose is 650 mg every 12 hours.

In another aspect the present invention provides an oral solid pharmaceutical composition

comprising at least 300 mg acetylsalicylic acid in sustained release form and capable of providing in the steady state on administration of an acetylsalicylic acid daily dose of 2.6 g in divided doses 2 or 3 times a day a significantly higher blood plasma free salicylic acid concentration than that obtained on administration of immediate release acetylsalicylic acid tablets at the same daily dose in divided doses every 4 hours.

Conveniently the pharmaceutical composition contains 300 to 700 mg ASA and has dissolution rate at 37°C in water of from 15 to 40 per cent in 1 hour and not less than 70% at 8 hours.

Preferably in 1 hour from 20 to 35 per cent is released. Conveniently at 8 hours from 70 to 90 per cent e.g. 80 to 90 per cent is released.

The following examples illustrate the invention.

In the Examples:

Microcrystalline cellulose has a molecular weight of from 30,000 to 50,000: mean particle size 30–100 microns; specific gravity 1.55; tap volume 0.30 to 0.80. The material used was the brand Avicel PH 102 (Registered Trade Mark) available from FMC Corporation, Marcus Hook, USA. It complies with specifications given for microcrystalline cellulose in USP/National Formulary XXI.

Hydroxypropyl methylcellulose 2208 has a number average molecular weight of 120,000; viscosity approx. 15,000 cps: a 19–24 per cent by weight methoxyl content and a 4–12 per cent by weight hydroxypropyl content. Used was brand Methocel K15M Premium (Registered Trade Mark) available from Dow Chemical Company Michigan USA. It complies with specifications given for hydroxypropyl methylcellulose 2208 in USP XXI.

Pregelatinized Starch is a modified corn starch and comprises 5 per cent amylose, 15 per cent amylopectin and 80 per cent unmodified corn starch. It is partially cold water soluble. The material used was the brand Starch 1500 (Registered Trade Mark) available from Colorcon Inc., West Point, Pennsylvania, USA. It complies with the specifications given for pregelatinized starch in USP/National Formulary XXI.

Colloidal silicon dioxide was the brand Cab-O-Sil (Registered Trade Mark) available from Cabot Corporation, Boston, Mass. USA. It complies with the specifications given in USP/National Formulary XXI.

The ASA used are 40 mesh crystals. The immediate release formulation used as reference in the bioavailability trials was brand Bayer Aspirin (Registered Trade Mark).

Further specifications for the above products are available in Manufacturer's brochures and in Lexikon der Hilfsstoffe by H.P. Fiedler, Second Edition 1981, Editio Canton, Aulendorf, W.Germany.

All other ingredients used meet the specifications laid down by the USP XXI.

EXAMPLE 1: 325 mg ASA tablets

	mg/tablet
ASA	325.000
Microcrystalline cellulose	47.500
Hydroxypropyl methylcellulose	27.625
Pregelatinized Starch	22.100
Stearic Acid	2.125
Colloidal Silicon Dioxide	0.650

A charge to make up 1 million tablets is made up as follows:—

The above quantities are multiplied by 1 million, e.g. 325 kg acetylsalicylic acid are used. 50 kg of acetylsalicylic acid are mixed with the silicon dioxide. The remaining acetylsalicylic acid, hydroxypropyl methylcellulose, silicon dioxide/acetylsalicylic acid mixture, microcrystalline cellulose and pregelatinized starch are introduced in an alternating fashion into a 30 cubic feet twin shell blender. Mixing is effected for 15 minutes. 40 kg of the mixture is removed. The remaining mixture is passed through a 20 mesh (aperture size 1.00 mm; wire diameter 0.63 mm) stainless steel screen on an oscillating granulator. The 40 kg unscreened mixture and the stearic acid are mixed for 5 minutes, screened through a 20 mesh stainless steel screen as described above with an oscillating granulator, and mixed with the previously screened mixture. Mixing is effected for 15 minutes using a tumbling action to produce a granulate. The granulate is then tabletted on a rotary tablet press. Tablet weight 425 mg. Thickness 4.68–4.85 mm. Hardness 8–12 Kiloponds (Heberlein method).

Dissolution release data (average of 6 tablets) in water at 37°C.

	Per cent release of ASA	
	Lot 1	Lot 2
1 hour	23.1	30.3
2 hour	39.4	45.4
3 hour	51.2	57.0
4 hour	61.4	65.9
6 hour	72.5	76.5
8 hour	80.7	86.6
12 hour	87.1	93.6

EXAMPLE 2: 650 mg ASA tablets

In analogous manner to that disclosed in Example 1 are produced tablets each containing:

	mg/tablet
ASA	650.000
Microcrystalline cellulose	95.000
Hydroxypropyl methylcellulose	55.25
Pregelatinized Starch	44.20
Stearic Acid	4.25
Colloidal Silicon Dioxide	1.30

The batch size is for 500,000 tablets. The resultant tablets have a weight each of 850 mg and thickness 6.25 to 6.40 mm.

Dissolution release data (average of 6 tablets) in water at 37 °C:—

	Per cent release of ASA	
	Lot 1	Lot 2
1 hour	21.5	26.8
2 hour	34.4	39.9
3 hour	44.2	49.8
4 hour	53.4	57.7
6 hour	66.1	69.0
8 hour	75.7	77.1
12 hour	86.9	85.7

Trial A:

Steady State Bioavailability of 1300 mg ASA according to the invention administered 3 times a day

The pharmaceutical composition of the invention described in example 2 (650 mg ASA tablet) was administered at a dose of 2 tablets to 12 healthy male volunteers at 7 am, 3 pm and 11 pm on days 1 to 8 and at 7 am on day 9. The total daily dose was 3.9 g ASA.

An immediate release formulation was given at a dose of 325 mg tablets every 4 hours from 7 am to 11 pm on days 1 to 8 and at 7 am and 11 am on day 9. The total daily dose was 3.25 g ASA.

Each subject received the two formulations in a 9 day study session according to a random sequence. The wash-out period at the end of the study session was 6 days.

Blood samples were obtained on day 8 at 7 am (pre-dose) and 11 am (pre-dose) and on day 9 at 7 am (pre-dose) and 1, 2, 3, 4 (pre-dose) in the case of the immediate release formulation),

5, 6, 8, 10 and 12 hours following drug administration at 7 am.

Statistical evaluation for both formulation on days 8 and 9 indicated that both were at the steady state for the day 9 bioavailability study.

The results obtained for the measurement of free plasma salicylate in the blood were as follows (REFERENCE=immediate release formulation):—

Results:

Day 9 (Steady-State)
Mean Plasma Salicylate
Concentrations (mcg/mL)

Sampling Time (hour)	3.9 G/day EXAMPLE 2 2 x 650 mg q8h	3.25 G/day REFERENCE 2 x 325 mg q4h
0	113.90 ± 56.14*	56.29 ± 36.90
1.00	117.91 ± 56.02*	68.55 ± 37.07
2.00	114.17 ± 57.27*	72.53 ± 31.12
3.00	118.58 ± 61.07*	68.54 ± 39.81
4.00	117.15 ± 59.25*	54.49 ± 32.29
5.00	115.66 ± 58.85*	67.02 ± 27.50
6.00	111.82 ± 57.34*	64.28 ± 21.55
8.00	94.20 ± 57.19*	54.57 ± 29.53
10.00	82.82 ± 49.36*	41.94 ± 26.46
12.00	68.11 ± 52.07*	30.02 ± 23.23

* The two formulations differ statistically at the 5% level or greater.

Pharmacokinetic Indices for Salicylate at Steady-State (Day 9)

	EXAMPLE 2 2 x 650 mg q 8 h	REFERENCE 2 x 325 mg q4h
0 - 8 hr AUC (mcg-hrs/mL)	902.35 ± 456.88*	510.26 ± 227.46
C_{max} (mcg/mL)	128.00 ± 60.54*	83.81 ± 33.20
T_{max} (hours)	3.08 ± 1.51	3.42 ± 1.88
$t_{1/2}$ (hours)	10.15 ± 5.38*	5.00 ± 2.37˜
K_{el} (hours^{-1})1)	0.09 ± 0.04*	0.17 ± 0.09˜

* Statistically different at the 5% level or greater.

˜ Calculation on numbers after second dose.

1) Elimination constant

Relative 0 - 8 hr AUC (%)	177.26 ± 57.61
Relative C_{max} (%)	153.18 ± 47.92

Evaluation of results

Statistical evaluation of steady-state plasma salicylate concentrations using appropriate statistical tests (paired t-tests) showed significantly higher plasma concentrations for the Example 2

formulation at every time point. The increase in plasma free salicylate levels is greater than predicted even if a 3.9 gram dose of the reference formulation had been administered. Statistical evaluation showed that the mean 0–8 hours AUC and mean C_{max} were significantly higher for the Example 2 formulation. Adjustment of the mean 0–8 hour AUC to a 3.9 g/dose for each product provides an estimated relative bioavailability of the Example 2 formulation of the invention of 147 per cent that of the reference product. The Example 2 formulation of the invention showed a significantly longer half-life and smaller K_{e1}.

The total salicylate concentration in urine was measured over 24 hours on day 9. Values obtained for the Example 2 formulation were 1488.42±531.08 mg and for the reference formulation 1265.97±572.16 mg. These values are similar.

Trial B:
Steady-State Bioavailability of 1300 mg ASA according to the invention administered twice a day

The Example 2 formulation (650 mg ASA tablet) was administered at a dose of 2 tablets to 6 healthy male volunteers. 3 of whom had completed the previous trial A at 7 am and 7 pm for 8 days with a final dose at 7 am on day 9. The total daily dose of ASA was 2.6 g. The protocol was the same as that discussed above except for the lower dose.

Statistical evaluation on day 8 and day 9 indicated that the steady state had been achieved by day 9.

The results obtained up to 12 hours after drug administration are given below:

Sampling Time (hour)	Day 9 (Steady-State) Mean Plasma Salicylate Conc. (mcg/mL) Example 2 2 x 650 mg q12h
0	49.70 ± 21.16
1.0	54.82 ± 22.75
2.0	58.72 ± 22.53
3.0	62.19 ± 23.31
4.0	59.90 ± 23.18
5.0	55.87 ± 25.84
6.0	55.18 ± 22.04
8.0	47.22 ± 24.77
10.0	42.98 ± 24.19
12.0	34.72 ± 20.09

The 0–8 hour AUC was calculated as 466±182.46 mcg-hours/ml. C_{max} was 64.11±21.78 (mcg/ml).

The results indicate that the dose of 2.6 g ASA given as a dose of 1300 mg ASA twice a day in a formulation according to the invention provides comparable plasma free salicylate levels to the immediate release formulation at a dose of 3.25 g ASA given as a dose of 650 mg ASA five times a day.

Urine total SA concentrations are also measured over a 24 hour period. The cumulative total SA was 1322±162 mg. This value is similar to the values found in Trial A.

CLAIMS

1. A process for the production of a sustained release pharmaceutical composition which comprises mixing a pharmacogically active agent and a) microcrystalline cellulose and b) hydroxypropyl methylcellulose wherein the weight ratio of a) to b) is at least 1 to 1. With the proviso that when the active agent is other than acetylsalicylic acid in free form or salt form the active agent is also in admixture with pregelatinized starch.
2. A process according to claim 1 wherein the active agent is acetylsalicylic acid.
3. A process according to claim 2 wherein tablet unit dosage forms are produced containing from 300 to 700 mg acetylsalicylic acid.

4. A sustained release pharmaceutical composition comprising a pharmacologically active agent in admixture with a) microcrystalline cellulose and b) hydroxypropyl methylcellulose wherein the weight ratio of a) to b) is at least 1 to 1.

5. A composition according to claim 4 wherein the active agent is acetylsalicylic acid.

6. A composition according to claim 4 or 5 in the form of a tablet.

7. A composition according to any one of claims 4 to 6 wherein the amount of acetylsalicylic acid per tablet is from 300 to 700 mg.

8. A composition according to claim 7 wherein the amount of acetylsalicylic acid is 325 mg.

9. A composition according to claim 7 wherein the amount of acetylsalicylic acid is 650 mg.

10. A composition according to any one of claims 4 to 9 wherein the microcrystalline cellulose has a mean polymerisation number of from about 200 to 2000.

11. A composition according to any one of claims 4 to 10 wherein the mean molecular weight of the microcrystalline cellulose from about 20,000 to 100,000.

12. A composition according to any one of claims 4 to 10 wherein the mean molecular weight of the microcrystalline cellulose is from 30,000 to 50,000.

13. A composition according to any one of claims 4 to 12 wherein the particle size of the microcrystalline cellulose is from 1.40 to 1.60.

14. A composition according to any one of claims 4 to 13 wherein the microcrystalline cellulose is brand AVICEL.

15. A composition according to any one of claims 4 to 14 wherein the methoxy content of the hydroxypropyl methylcellulose is from about 15 to about 34 per cent by weight.

16. A composition according to any one of claims 4 to 15 wherein the methoxy content of the hydroxypropyl methylcellulose is from 19 to 24 per cent by weight.

17. A composition according to any one of claims 4 to 16 wherein the hydroxy content of the hydroxypropyl methylcellulose is from about 4 to about 32 per cent by weight.

18. A composition according to any one of claims 4 to 17 wherein the hydroxy content of the hydroxypropyl methylcellulose is from about 4 to 12 per cent by weight.

19. A composition according to any one of claims 4 to 18 wherein the viscosity of the hydroxypropyl methylcellulose is about 15 to about 50,000 cps (based on a 2 per cent by weight aqueous solution at 20 degrees centrigrade).

20. A composition according to claim 19 wherein the viscosity of the hydroxypropyl methylcellulose is 4000 to 50,000 cps.

21. A composition according to any one of claims 4 to 20 wherein the mean molecular weight of the hydroxypropyl methylcellulose is from about 20,000 to 200,000.

22. A composition according to any one of claims 4 to 21 wherein the mean molecular weight of the hydroxypropyl methylcellulose is 90,000 to 130,000.

23. A composition according to any one of claims 4 to 22 wherein the hydroxymethyl cellulose is brand Methocel.

24. A composition according to any one of claims 4 to 23 wherein the weight ratio of microcrystalline cellulose to hydroxypropyl methylcellulose is from 10:1 to 1:1.

25. A composition according to any one of claims 4 to 24 wherein the weight ratio of microcrystalline cellulose to hydroxypropyl methylcellulose is from 3:1 to 1:1.

26. A composition according to any one of claims 4 to 25 wherein the weight ratio of microcrystalline cellulose to active agent is from 1:5 to 1:10.

27. A composition according to any one of claims 4 to 26 wherein the weight ratio of microcrystalline cellulose to active agent is from 1:6 to 1:7.5.

28. A composition according to any one of claims 4 to 27 comprising gelatinized starch.

29. A composition according to any one of claims 4 to 28 wherein the weight ratio of pregelatinized starch to hydroxypropyl methylcellulose is from about 1:1 to about 1:5.

30. A composition according to any one of claims 4 to 29 wherein the weight ratio of active agent to all other excipients present is from 2:1 to 4:1.

31. A composition according to any one of claims 4 to 30 in the form of a tablet compressed to a hardness of about 8 to 12 kiloponds.

32. An oral solid pharmaceutical composition comprising at least 300 mg acetylsalicylic acid (ASA) in sustained release form and capable of providing in the steady-state on administration of an acetylsalicylic acid dose of 2.6 g in divided doses 2 or 3 times a day a significantly higher blood plasma free salicylic acid concentration than that obtained on steady-state administration of immediate release acetylsalicylic acid tablets given at the same daily dose in divided doses every 4 hours.

33. A composition according to claim 32 wherein the pharmaceutical composition contains 300 to 700 mg ASA and has dissolution rate at 37°C in water or from 15 to 40 per cent in 1 hour and not less than 70% at 8 hours.

34. A composition according to claim 32 or 33 wherein the composition is in the form of a tablet.

35. A composition according to claim 32, 33 or 34 wherein the composition is in the form

of a tablet compressed to a hardness of about 8 to 12 kiloponds.

36. A composition according to claim 35 wherein the composition is characterised by a feature of any one of the claims 4 to 30.

37. A composition substantially as hereinbefore described with reference to any one of the examples.

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